

REMARKS

Claims 1-120 are canceled, claim 121 has been amended, and new claims 122 - 130 have been added. Claims 121 - 130 are now pending for the Examiner's consideration.

Claim 121 has been rewritten in independent form. New claims 122-130 recite particular embodiments and are supported, for example, by Example 3 of the application as filed. No new matter is added.

Applicant respectfully requests favorable consideration of the pending claims.

1. Entitlement to Priority

The Examiner has not accorded claims 107, 111 and 113-120 the benefit of the priority document, U.S. Provisional Application No. 60/421,133 as the priority document allegedly lacks support or enablement under 35 U.S.C. §112 for these claims. Without acquiescing on the merits, and in order to expedite prosecution, by the present amendments claims 107, 111 and 113-120 have been canceled without prejudice. Claim 121, and new claims 122-130, are supported in Example 3 of the present application, and are supported in Example 3, page 64, of the priority document 60/421,133. Accordingly, applicants believe all pending claims are entitled to the benefit of 60/421,133, filed September 10, 2002.

2. Rejection under 35 U.S.C. § 112

Claims 107, 113, 115-117 and 120 were rejected under 35 U.S.C. § 112, second paragraph, for the reasons set forth on pages 3 and 4 of the Office Action. These claims have now been canceled.

Claim 121 was rejected under 35 U.S.C. § 112, second paragraph, as being dependent upon itself. By the present amendments, claim 121 has been rewritten in independent form.

Accordingly, applicants believe all of the rejections under § 112 have been overcome, and request that they be withdrawn.

3. Rejections under 35 U.S.C. § 102

Claims 107, 113, 115-118, 120 and 121 were rejected under 35 U.S.C. § 102(a) and 102(e) as being anticipated by International Patent Publication WO 03/035009 to O'Farrell et al., for the reasons set forth on page 5 of the Office Action. These same claims were rejected under § 102(a) and § 102 (e) over the corresponding O'Farrell U.S. application publication, US 2003/0130280 for the reasons set forth on pages 5-6 of the Office Action. All of these

claims, with the exception of claim 121 have been canceled. As to claim 121, Applicants respectfully traverse.

As discussed above, claim 121 is entitled to the benefit of its priority application, 60/421133, filed September 10, 2002. WO 03/035009 was filed October 28, 2002, claiming priority to a U.S. provisional application, 60/330,623 (“the ‘623 provisional”) filed October 26, 2001. US 2003/0130280 was filed October 28, 2002, and also claims priority to the ‘623 provisional. However, The ‘623 provisional discusses formulations generally, but does not disclose the formulation of claim 121. In particular, Table 3 in the O’Farrell publications was added to the specification in the U.S. regular application filing and in the PCT filing, but is not present in the ‘623 Provisional. Thus, the disclosure of the O’Farrell Table 3 is only entitled to the priority date of October 28, 2002, in both the PCT and US application publications. Since this date is later than the September 10, 2002 priority date of claim 121, the disclosure of the ‘623 provisional does not disclose the invention of claim 121, there can be no anticipation. Applicant respectfully requests that the rejections under § 102(a) and § 102(e) over WO 03/035009 and US 2003/0130280 be withdrawn.

4. Rejections under 35 U.S.C. § 103

Claims 107, 111, 113 and 115-121 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 01/37820 A2 to Shenoy et al. (“Shenoy”) in view of US 4,609,675 to Franz (“Franz”) and US 6,077,533 to Oshlack et al. (“Oshlack”) for the reasons set forth on pages 6-12 of the Office Action. All of the rejected claims except claim 121 have been canceled. With regard to claim 121, Applicants respectfully traverse.

Shenoy reference is directed to formulations of “an ionizable substituted indolinone” which is “*necessarily* substituted on the pyrrole moiety with one or more hydrocarbon chains which themselves are substituted with at least one polar group” (emphasis added; see WO 01/37820 Abstract). The compound recited in the current claims has three substituents on the pyrrole group: two methyl groups and an amide. It is not substituted with a hydrocarbon chain which is further substituted with a polar group. As noted throughout the Shenoy specification, the preferred compound, and the only compound for which examples are shown, is 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid (Compound IV; see page 29), a compound which has a propionic acid substituent on the pyrrole ring. This important structural difference results in a compound

which is an acidic, ionizable, hydrophobic compound (pKa 5.02; see page 226, lines 4-5). The aqueous solubility of the free acid compound ranges from 0.0024 to 1.6 mg/mL at pHs of from 6.0 to 9.0 (Table 4, page 225), and the highest solubility reported is 17-25 mg/mL for the sodium salt at a pH of 8.6-8.9. It is these properties (hydrophobic, ionizable) which drive the formulation development (see page 224, lines 13-14, and page 226, lines 11-15), which relies on the sodium salt or an in-situ sodium salt formation (see Example 3).

In contrast, the compound recited in the present claims is a weakly basic compound (pKa 8.95) with relatively good water solubility. A direct comparison of the aqueous solubility of the Shenoy propionic acid compound and the compound recited in the present claims can be found in Table 1 of *J. Med. Chem.* 2003, 46, 1116-1119, a copy of which was submitted with Applicant's response of August 8, 2006. As the Table shows, under the conditions described in footnote (b), the Shenoy propionic acid compound (Compound 5b) has a pH 2 solubility of less than 5 µg/mL compared to 2582 µg/mL for the compound of the present claims (Compound 12b). At pH 6, the solubilities are 18 µg/mL and 364 µg/mL, respectively. The dramatically improved aqueous solubility of the presently claimed compound eliminates the need to rely on an in-situ salt formation strategy as is done with the propionic acid compound of Shenoy. Given the differences between the compounds, one skilled in the art would not look to the teachings of Shenoy, directed to formulations to enhance the solubility of hydrophobic, ionizable compounds, to provide a formulation for 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate, which has good aqueous solubility and would not be expected to have formulation challenges similar to those which Shenoy attempts to solve.

Further, even if one looked to Shenoy as a starting point, one would need to make numerous selections from the disclosure of Shenoy to arrive at the presently claimed invention, and it would not have been obvious to make such selections. Some of the selections include:

(1) Active agent: Shenoy discloses at least 260 compounds, with the preferred compound having a carboxylic acid moiety (propionic acid) on the pyrrole ring. The present claims include a compound having a diethylaminoethyl amide group on the pyrrole ring. There is no suggestion that would lead one of ordinary skill in the art to select the claimed

compound, having a basic terminal group (-N(Et)<sub>2</sub>), from the several hundred disclosed compounds having various functionalities, particularly in light of the preference for the propionic acid compound. Clearly, as a starting point for further modifications, one would have no reasonable choice but to start with the sole exemplified compound, the propionic acid compound. The disclosure of a list of more than 200 compound can not possibly provide the motivation to try each and every compound in each and every permutation of as many as 14 formulation components (Table spanning pages 92-93) to arrive at the presently claimed formulation.

(2) L-malate salt: Shenoy does not teach the malate salt of the present compound, but only lists various salts as possibilities for the disclosed compounds in general. Even if one were to select the presently claimed compound from the several hundred compounds disclosed in Shenoy, there is no teaching or suggestion that would direct one of ordinary skill in the art to choose the L-malate salt. Thus, at least a second selection must be made to arrive at the presently claimed invention.

(3) Solid formulation: Shenoy teaches various formulation types, and exemplifies parenteral formulations and oil suspensions in addition to solid formulations. Example 5 (page 229-231) of Shenoy compares the oral bioavailability of an oil-suspension formulation to that of a conventional wet granulated tablet, and shows that the oil-suspension provides a mean AUC of from three to four times that of the tablet, showing greater bioavailability. Clearly high bioavailability is desirable, and one of ordinary skill in the art would reasonably conclude from the Shenoy teaching that oil suspensions are preferred. Despite this apparent superiority of oil suspension dosage forms, one of ordinary skill in the art would need to choose instead a solid dosage form. Thus, at least a third selection must be made to arrive at the presently claimed invention, and Shenoy appears to teach away from this selection.

(4) Specific component amounts: As noted previously, Shenoy discloses an extremely broad range of concentrations for each of many possible components. In the table on page 96, for example, Shenoy discloses 5-90% active ingredient, with a “most preferred” range that is unhelpfully nearly as broad, 15-75%. This range is so broad as to be useless in guiding one of ordinary skill in the art to the specific amounts recited in the present claims. Further, as applicants have noted, the wrong choices give rise to inferior properties, such as poor bulk densities or sticking problems. Thus, in addition to the many choices already

outlined, one of ordinary skill in the art must make further choices in the amount of active ingredient and the specific components and amounts of such components to arrive at the presently claimed invention.

In light of the multitude of selections required from the broad disclosure of the Shenoy reference, Applicant believes the present claims would not have been obvious over Shenoy alone or in view of Franz and Oshlack. Neither Franz nor Oshlack provides guidance to select the presently claimed active ingredient or the L-malate salt thereof, or the specifically claimed narrow concentration references. Both Franz and Oshlack are directed to formulations of compounds chemically unrelated to the compound in the present claims.

Accordingly, Applicants believe the present claims would not have been obvious over Shenoy in view of Franz and Oshlack, and request that the rejection under §103 be withdrawn.

With specific reference to new claims 122 and 127-130, which recite that the composition consists essentially of the five claimed components, the composition necessarily does not include a flow enhancer or surfactant. Applicants point out that when Shenoy does choose to exemplify a solid formulation, as shown in Table 11 on page 233, Shenoy shows that with a 28% concentration of active ingredient, all of the exemplified formulations include 0.5% colloidal silicon dioxide, a flow enhancer, and either sodium lauryl sulfate or cetylpyridinium chloride as surfactants. In the Table on page 96 (bottom) that the Examiner relies on to show the broad ranges of components such as 15-75% active ingredient, both the “preferred” and “most preferred” formulations include at least 0.3% flow enhancer and at least 0.1% surfactant. Further, as shown in the Comparative Example of the present specification, Table 1, a composition having 75% active ingredient shows sticking problems, also suggesting the need for flow enhancer. Thus, it would not have been obvious at the time of the invention to prepare the formulation of claims 122 and 127-130, having an active ingredient concentration higher than that of Shenoy’s 28%, but without including a flow enhancer or surfactant.

Claims 107, 111, 113 and 115-121 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,573,293 to Tang et al. (“Tang”) in view of Shenoy and the two O’Farrell publications (WO 03/035009 and US 2003/0130280) for the reasons set

forth on pages 12-14 of the Office Action. All of the rejected claims except claim 121 have been canceled. With regard to claim 121, Applicants respectfully traverse.

Tang et al. issued on June 3, 2003, after the September 10, 2002 priority date of claim 121. Thus, Tang et al. is available as 103(a) prior art only under § 102(e). However, the subject matter of the claimed invention and Tang et al. were, at the time the claimed invention was made, owned by the same person (Sugen, Inc., a wholly owned subsidiary of Pharmacia & Upjohn, or Sugem and Pharmacia, respectively). Thus, under 35 U.S.C. § 103(c), Tang et al. is disqualified as 103(a) prior art, and Applicant respectfully requests that the rejection be withdrawn.

Applicant believes all claims are now in condition for allowance. Should there be any issues that have not been addressed to the Examiners satisfaction, Applicant invites the Examiner to contact the undersigned attorney.

If any fees other than those submitted herewith are due in connection with this response, including the fee for any required extension of time (for which Applicant hereby petitions), please charge such fees to Deposit Account No. 161445.

Respectfully submitted,

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